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(54) **Instrument and method for noninvasive testing for glucose and other body fluid constituents.**

(57) There is disclosed herein a nuclear magnetic resonance apparatus (10) for testing body fluids for a constituent, for example, testing blood for glucose. The apparatus includes a principal magnet, a magnetizable coil (38), and a circuit (40) for energizing the coil for energizing and realigning molecules and detecting changes resulting from relaxing molecules and detecting changes resulting from relaxation of said field and analyzing said changes. The apparatus is compact and adapted to receive and test an extremity or vessel carrying a body fluid. The coil is constructed to be positioned adjacent the extremity or vessel to be tested. Circuit means are provided for energizing the coil to energize and realign molecules adjacent said coil, so as to permit molecules adjacent said coil to assume an aligned position and for sensing changes in position when the coil is deenergized, which is indicated by spectra having peaks corresponding to various molecular bonds. The circuit also includes means for comparing the actual value of a peak for a first constituent to a predetermined value for the peak of said first constituent and determining the actual value of a second constituent from a predetermined relationship between the values of the peaks for the first and second constituents. Specifically, predetermined water and glucose peaks are compared with the measured water and glucose peaks for determining the measured glucose concentration.

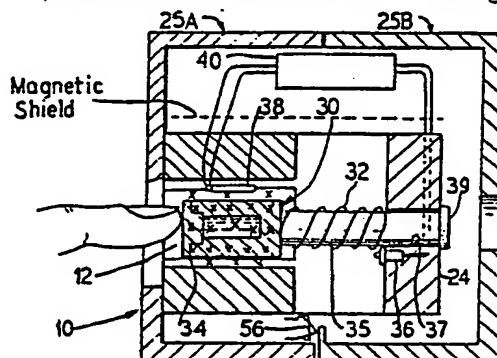


FIG. 2

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INSTRUMENT AND METHOD FOR NONINVASIVE TESTING FOR GLUCOSE AND OTHER BODY FLUID CONSTITUENTS

This invention primarily relates to a method and to an instrument for use in medical diagnosis, and in particular, to detecting and determining the concentration of a constituent in a body fluid.

Diabetes is a health problem affecting many individuals and its prevalence is increasing. The usual treatment for diabetes is single or multiple insulin injections daily. Insulin is available in slowly or rapidly absorbed forms, which may be injected alone or in combination. Such insulin injections have been effective in treating the disease and in prolonging life.

Presently in order to determine if insulin is needed, blood is withdrawn from a patient and is tested for glucose concentration by a litmus-type indicator test. If indicated, insulin is taken by the patient.

This type of testing has several problems. For example, the testing is periodic, and thus the administration of insulin is periodic, which can result in wide variations in glucose concentration over time and peaks in the glucose concentration. Such variations can have physiological effects which may be adverse to the patient.

It has been recognized that it is desirable to administer insulin periodically on demand and in response to changes in glucose levels. One such system is disclosed in Albisser A, "Devices for the Control of Diabetes Mellitus", Proc. IEEE 67 No. 9, 1308-1310 (1979), wherein a servo system is employed which continuously withdraws blood from a patient and analyzes the same for glucose. Using a computer or microprocessor, calculations are made from the withdrawn sample as to the need for insulin, and in response thereto, insulin is administered. This system has only been used for short periods and has a disadvantage in that the system is invasive (i.e., the patient is catheterized continuously for withdrawing blood samples).

The litmus-type system has the disadvantage that it is invasive and the patient is periodically and repeatedly pricked for blood samples.

It is therefore an object of this invention to provide a glucose testing device which can be used to monitor a patient's glucose level continuously, if desired, so as to provide a more uniform administration of insulin and a more uniform glucose concentration in the blood over time.

It is another object to provide a glucose monitoring system which is noninvasive and does not require periodic blood withdrawal to determine glucose levels.

It is sometimes desirable to test body fluids for other constituents. For example, law enforcement officers test individuals for alcohol content of their blood using a breathalyzer. However, breathalyzer tests may be inaccurate in that non-ingested alcohol, such as in mouthwashes, will provide false results.

It is another object of this invention to provide a noninvasive diagnosis apparatus for use in determining the concentration of various constituents of body fluids, such as glucose and alcohol and drugs.

Nuclear magnetic resonance (NMR) is a diagnostic technique which is used widely for medical imaging and medical diagnosis. In NMR, the test object is subjected to a first or biasing magnetic field to align previously randomly oriented ^1H protons in the nuclei and a second field or burst of energy to increase the energy of a selected nucleus. When the second magnetic field or energy source is turned off, the return to the first alignment releases energy which is detected and analyzed. This release is analyzed or processed to form an image or spectrum. From the spectrum, the presence of particular molecular bonds can be observed and associated with various molecules or materials from which the concentration of that molecule or material can be determined.

NMR machines are most frequently used for imaging sections of a human body and require large magnets, for example, superconducting magnets. The machines are therefore quite large and expensive. Furthermore, the NMR testing of fluids has required invasive sample withdrawal techniques, which sample was then tested in the larger machines.

Using such NMR machines, blood serum has been analyzed and spectra of the ^1H resonance developed. In such spectral identifiable peaks are obtained for water, glucose and ethanol. In reported tests, blood serum has been taken from animals, placed in a container and excited so as to yield the ^1H spectra, which are then analyzed. Unfortunately, NMR testings are not common nor conveniently available. The reason is believed to be that the equipment is generally large, complex and expensive, and is therefore available only at selected centers, such as hospitals, universities, and other similar research and test sites. The equipment therefore is not normally used for blood or body fluid analysis as more convenient and less expensive alternatives are available.

Another disadvantage in present NMR tests is that they are conducted on fluid samples which are withdrawn from the patient by the usual invasive techniques.

It is an object of this invention to provide a more convenient NMR Instrument for use in analyzing body fluid samples.

It is a further object of this invention to provide an NMR instrument for use in analyzing body fluid for glucose.

5 It is yet another object to provide a portable NMR instrument for use by a person having diabetes to analyze his blood for glucose concentration.

It is yet a further object to provide an NMR instrument for use by a diabetic in noninvasively analyzing his blood serum for glucose concentration.

10 It is a still further object of the invention to provide an NMR method and apparatus to test for other substances, for example, alcohol and drugs.

These and other objects of this invention will become apparent from the following disclosure and appended claims.

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SUMMARY OF THE INVENTION

This invention provides a method and a portable NMR instrument for use in noninvasively analyzing body fluids for the concentration of various constituents. Specifically, a diabetic can use the instrument to
20 noninvasively and substantially instantaneously analyze his blood for glucose, thereby eliminating the need to invasively obtain a blood sample which is then tested. Using the device disclosed herein, a patient can periodically, frequently if necessary, and painlessly analyze his blood for glucose concentration. This device may also be useful in analyzing body fluids for alcohol or drugs.

In one form, the device is portable and provided with means for receiving an extremity of the patient,
25 such as a finger, and exposing the extremity to a first or biasing magnetic field and a second field or energy source. Sensors are provided for sensing the rates of relaxation or energy release so as to develop the spectrum. Analytical means are coupled to the sensors for receiving and analyzing the signals emitted, discriminating between various peaks, comparing the amplitude or height of various peaks, such as water and glucose, and normalizing the analysis by reference to a standard sample so as to obtain the
30 concentration of constituents in the tested materials.

One of the principal components of the preferred NMR instrument is the first or biasing magnet for providing the first magnetic field. In this device the biasing magnet is a permanent magnet and is physically much smaller than the magnets used in standard NMR machines. For example, the magnet may be one
35 pound (450 g) in weight and may exhibit a field strength of at least five to six kilogauss. Another component is a coil apparatus for applying a second field or energy to the test sample and sensing the energy released therefrom. A single coil or multiple coils can be used. Yet another important element of this invention is the electronic circuit used for the analysis. This circuit is controlled by a microprocessor that is programmed to control the application of the second field or energy source and cooperates in detecting and analyzing the spectra received from the sample when the field is relaxed. Operation of the microprocessor is disclosed
40 herein.

Other specific features of the instrument are disclosed hereinafter.

Certain embodiments of the invention will now be described by way of example only and with reference to the accompanying drawings.

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BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is a vertical cross-sectional view of an instrument according to this invention;
50 FIGURE 2 is a vertical cross-sectional view taken along line 2-2 of Fig. 1 and also showing a housing and other components;
FIGURE 3 is a block-type schematic diagram for the circuitry to operate the instrument;
FIGURES 4a to 4c are flow charts showing the operation of the instrument;
FIGURES 5a and 5b are representative NMR spectra showing the water, glucose peaks and alcohol
55 used for analysis;
FIGURE 6 is a schematic diagram showing a three-coil system for use in the instrument;
FIGURE 7 is a schematic diagram showing the electrical connections for the three-coil system of Fig. 6;
6;

FIGURE 8 shows an NMR probe for implantation in a body;

FIGURE 9 is a schematic block-type diagram of the electrical circuit for use with the implantable probe of Fig. 8;

FIGURE 10 shows a human arm having a distended vein for NMR testing;

FIGURE 11 is a fragmentary and sectional view of a magnetic probe for use in NMR analysis using a surface blood vessel;

FIGURE 12 is a schematic representation of an alternative circuit arrangement for use with separate energizing and receiving coils;

FIGURE 13 is a schematic representation of the coil and magnet relationships which may be used in an arrangement of the type shown in Fig. 12;

FIGURE 14 is a schematic representation of a multi-coil arrangement;

FIGURE 15 is a top view of the elements of Fig. 14; and

FIGURE 16 is a side view of an alternative C-shaped magnet which may replace the magnetic structure of Figs. 1 and 2.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring now to Figs. 1-3, a first embodiment of the test instrument is shown. Other embodiments and features will be discussed after consideration of principal features of this invention by way of the first embodiment.

The test instrument 10 is shown as including a box-shaped assembly which defines a finger-receiving recess or test region 12 therein. The assembly includes a body section 14 defined by the top, bottom and elongated side walls 16, 18, 20 and 22 and the back wall 24. The assembly is enclosed in a two-piece cover or housing 25A and 25B within which the electronic components discussed hereinafter are also enclosed. Alternatively, the electronics can be enclosed in a separate housing connected to the body section. A pair of first or biasing permanent magnets 26 and 28 form the top and bottom walls 22 and 18, are positioned opposite one another and provide the first aligning magnetic field. It is to be noted that the poles of the respective magnets are aligned so that the field is additive, and the pole pieces or shoes shape the magnetic field in the finger-receiving recess 12. This alignment is shown by the "X" designation, which indicates that the magnetic field from the magnets passes through the recess 12 in the same direction, in Fig. 2, into the paper.

A sample holder or container 30 for a standard sample and for starting the apparatus is shown positioned in the recess. The apparatus includes a compression biasing spring 32 pressing at one end against the back wall 24 and against a standard holder 34 at the other end. The holder 34 is mounted on a post-like member 35, which is guided through an aperture 37. A start switch 36 is mounted to the back wall offset from the member 35 so that when the standard holder 34 is pushed against the spring toward the back wall, the holder will depress the start switch to start operation of the instrument. Release of the standard sample holder will release the switch. The switch may also be mounted outside, say beneath the head 39, and operated upon movement of the head 39. The holder 34 holds a reference sample of known concentration which is sealed in at the time of manufacture.

A surface coil 38 is mounted in the housing adjacent one of the permanent magnets 26 and 28. The coil produces the second field and acts as a source of energy for realignment and for sensing purposes. As seen in Fig. 1, the second field produced by the surface coil is transverse to the first or permanent magnet field. The surface coil has been selected for this embodiment because the depth of magnetization (i.e., extent of penetration of the field) is related to the diameter of the coil and can thus be controlled.

The surface coil 38 may be a single coil for both energization and sensing. The coil can also be an assembly in which there are multiple coils, each of which are for energization and sensing. Furthermore, the coil may be an assembly of at least two coils, where at least one is for energization and at least one other coil is for sensing. These alternatives are shown in Figs. 13, 14 and 15.

The cover or housing 25A and 25B for the electronics is provided with an electronic interlock system (schematically shown as 56 in Fig. 3) so that unauthorized opening or removal of the cover will disable the electronics described hereinafter, thereby preventing unauthorized tampering or repair of the device which could destroy calibration and result in improper usage.

Physically the test is run by the patient inserting his finger into the instrument and pushing the sample holder toward the back wall 24 and into engagement with the start switch 36 to start the analysis as described hereinafter.

It will be noted that the finger is positioned so that the fingernail is located adjacent the surface coil.

This positioning is chosen as the fingernail is dead tissue but has a bed of active blood vessels positioned just below the nail. These vessels are believed to provide an accurate testing site. In many other test sites, live body tissue or bone must be penetrated in order to test blood in a vessel, which means that the tissue or bone will emit signals due to testing which act as noise and may interfere with analysis of the blood for glucose concentration. The finger region is preferable, since the nail is essentially dead material and produces little, if any, interfering noise, thereby increasing the signal to noise ratio. It is believed that other body extremities can be tested, for example, the ear of either a human or other animals.

The testing circuit 40 includes a battery power supply 42. In a permanent installation, such as a doctor's office, hospital, etc., a commercial AC power supply and battery charger may be used to supply energy to the battery. Depression of the start switch activates the circuit and thereby the microprocessor 44. The microprocessor activates an RF generator and cyclically-operated gate 46, which excites the surface coil 38 (or coil assembly) for applying the second field, raising the energy state and realigning the nuclei.

At the appropriate time and under control of the microprocessor, the RF generator is deactivated, thereby permitting the nuclei (dipoles) to relax or return to the first alignment. The surface coil then detects the energy released during relaxation and realignment. Those signals are received by receiver/gate 48, converted from analog signals to digital signals by the A/D converter 50 and fed to the microprocessor 44. A read only memory (ROM) 52 is provided for storing the program for use with the microprocessor in calibrating the machine and analyzing and displaying test results. If separate coils are used, then the circuit is changed so that the RF generator is connected to the energizing coil and the receiver is connected to the sensing coil as shown in Fig. 12.

The ROM is continuously energized by the battery 54. A cover interlock switch 56 is provided between the ROM 52 and battery 54 to deenergize the ROM in the event the electronics cover 25A or 25B is opened, removed or tampered with. In such an event, the switch 56 is opened and the program in the ROM is erased. In this instance, the ROM may be selected from the well-known classes of electrically erasable or alterable ROM'S. The specific function of the ROM-cover interlock arrangement may be selected as desired, i.e., to generate an error message on the panel display, or simply to disable the apparatus from operating or exhibiting any panel display. Various other forms of electronic-type interlocks are well-known in the computer art.

The testing circuit 40 also includes a display 58, preferably digital, which is connected to the microprocessor and a group of status lamps (read 60, calibrate 62, display 64 and error 66), which indicate the status of the system's operation.

The ROM 52 includes a program as represented by the flow chart of Figs. 4a-4c, whereby operation of the tester is controlled. In general, the operation of the tester is as follows:

1. A finger is inserted to depress the standard sample holder and activate the start switch.
2. The finger is tested.
3. The finger test results are stored in the RAM 45.
4. The finger is released and the standard sample moved to the test position.
5. The standard sample is tested.
6. The standard sample test results are stored in the RAM 45.
7. The standard sample test results are compared with predetermined calibration data, previously entered in memory, to determine if the standard sample data reading is still within preset and allowable tolerances.
8. Then the finger test results are compared with the sample standard test result data and the finger data is normalized and proportioned to determine glucose concentration.

Referring now to the flow diagram, Figs. 4a through 4c, the various phases of the microprocessor and ROM are shown. These phases can be considered as follows:

1. Patient reading cycle.
2. Standard sample reading cycle.
3. Operational system check.
4. Calculation of normalized patient data and standard sample for equal H₂O peak.
5. Calculation of glucose level. Within each one of these broad steps are a series of smaller steps.

Referring first to Fig. 4a, the flow chart begins with depression of the starting switch 36, initiation of the program and activation of the read light 60. Next, a one second homodecoupling pulse (or a plurality of pulses) to saturate the water peak is activated. A five microsecond sample pulse is taken, and the free induction decay output from the A/D converter is noted. Next, the data points are stored in the memory 45 and the process is repeated (i.e., looped) perhaps one hundred times. In the right-hand column, there is shown a series of diagrams representing the one second homodecoupling pulse, the five microsecond

sampling pulse, the decay, and a Fourier transformation of the decay data points. The amplitude (Amp.) of the response is recorded along the Y-axis. After the samplings, the read lamp is deactivated, the accumulated responses are multiplied by an exponential decay to provide line broadening, a Fourier transformation is run, and a spectrum is stored as the chemical shifts versus the peak height as patient data.

Turning now to Fig. 4b, the standard sample reading cycle is next activated. Here the calibrate light is turned on, and the start switch is released. Once the switch is released, a one second homodecoupling pulse (or plurality of pulses) is provided, a five microsecond sampling pulse is taken, the free induction decay is recorded, and the data points are stored in the memory 45. The process is then repeated again, perhaps one hundred times. As in the patient reading cycle, the accumulated responses are multiplied by an exponential decay to improve line broadening, Fourier transforms are run and the spectrum of chemical shifts versus peak height is stored as sample data.

The standard sample initially contains predetermined amounts of the constituent material or materials being tested for and acts as a reference level. In order to assure that there has been no significant change in the sample value(s), the next step is an operational check where the spectrum of chemical shifts versus peak height data for the standard sample is recalled and compared to the standard data previously taken within allowable tolerances. If the error is not within an acceptable tolerance, the error display lamp 66 is lit and the operator notified. If the data is within an allowable error, the system proceeds to the next step. It is noted that on the right-hand side of Fig. 4c a comparison is shown between the standard sample data and standard sample spectrum showing the allowable shifts, peak height and frequency with amplitude plotted along the Y-axis.

The next step is to normalize the patient data and standard sample data for equal water heights. Here the patient data is recalled and the standard sample data is recalled. Next, the patient data water peak height is scaled to match the standard sample data water peak height.

The system then executes the next step which is to calculate the glucose level. To do this a ratio is obtained of the patient data glucose peak height and the standard sample data peak height. This ratio is then multiplied by the known standard sample glucose to water ratio to obtain the patient reading and multiplied by a concentration_factor (K) from the standard sample and expressed in milligrams per deciliter or some other convenient unit. Then the patient glucose level is displayed in relation to plasma level. Normal glucose concentration is ninety milligrams per deciliter.

This relationship is derived as follows:

1. The standard sample is prepared having a known glucose concentration expressed, for example, in milligrams of glucose/deciliter of water (mg/dl) and referred to as K.
2. A patient is tested and the water and glucose peak heights are obtained.
3. The standard sample is then tested for water and glucose peak heights.
4. The patient's water peak height is normalized by determining the ratio of water standard peak height/water patient peak height. This ratio can be referred to as gain.
5. The patient's glucose peak height is normalized by multiplying the patient glucose peak height by the gain. The result is the normalized patient glucose level. Expressed algebraically:

$$\text{Glucose normalized} = \frac{(\text{Water standard})}{(\text{Water patient})} \times \text{glucose patient}$$

6. In order to obtain the actual patient glucose concentration, expressed in units such as mg/dl, the normalized glucose now is divided by the glucose standard and the resulting ratio is multiplied by the concentration factor K. In other words:

$$\text{Patient glucose concentration} = \frac{\text{Glucose normalized}}{\text{Glucose standard}} \times K$$

7. The entire expression which combines the steps of numbers 1-6 above can be stated as:

$$\frac{\text{Patient glucose concentration (mg/dl)}}{\text{(Glucose patient) (peak height)}} = K \frac{\text{(Water standard) (peak height)}}{\text{(Water patient) (peak height)}}$$

5

$$\times \frac{\text{(Glucose patient) (peak height)}}{\text{(Glucose standard) (peak height)}} = K \frac{\text{(Water standard) (peak height)}}{\text{(Water patient) (peak height)}}$$

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In Fig. 5a, a ^1H typical blood spectrum is shown with the water (H_2O) and glucose peaks clearly shown. It is the ratio for the peak heights as determined from the calibration and test samples that permit determination of the test sample glucose concentration. Fig. 5a shows the work of Jay Block, "Analysis of Serum by High Yield NMR", Clin. Chem. 28/9, 1983, (1982) taken from normal blood serum. Sample volume is 0.4 ml serum to which has been added 0.1 ml of $^2\text{H}_2\text{O}$ for field lock. In addition, 10 mmol/l of TSP was added to the $^2\text{H}_2\text{O}$ to serve as a reference to assign chemical shifts and peak area. The work was done on a WM 500 Bruker spectrometer. Samples were maintained at 30°C and a 1 second homodecoupling pulse was applied before the 5 millisecond samples pulse (45° notation angle) to saturate and reduce the H_2O peak. A total of 16K data points was recorded in an acquisition time of 1.5 seconds with 80 such transients averaged for each spectrum (2 min per spectrum). Even with the water peak suppressed, it is still the most prominent feature; however, the glucose peak which is four orders of magnitude lower is still easily identified. The glucose concentration is in the normal range of 90 mg/dl as measured by the conventional glucose oxidase procedure. Lactate was also detectable. It is also interesting to look at the glucose peak at 5.25 in the otherwise peak free region.

Fig. 5b is an enlarged portion of the ^1H blood spectrum of Fig. 5a, showing the ethanol and water peaks, as also reported by Bock and showing the spectrum of serum obtained 30 minutes after ingesting 30- ml of vodka. The ethanol concentration measured by routine gaschromatographic method was only 30 mg/l, while the methyl resonance of ethanol at 1.20 ppm was detected with better than 40:1 signal to noise ratio. The methylene resonance is buried in the glucose region. In addition, a large peak appears at 1.93 ppm, the position of acetate, presumably derived from the oxidation of ingested ethanol. In serum from intoxicated patients, the ethanol resonance had a much greater intensity and dominated the spectra.

For alcohol the relation is:

$$\frac{\text{Alcohol concentration (mg/dl)}}{\text{(Alcohol patient peak height)}} = K \frac{\text{(Water standard peak height)}}{\text{(Water patient peak height)}}$$

40

45

wherein

50

K = concentration of alcohol in said standard sample expressed in mg/dl.

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Another embodiment 70 of this invention is shown in Fig. 6. In this embodiment, three coil pairs 72, 74, and 76, are provided, which lie with their axes in the same plane and are equally spaced, that is at equally spaced 60° intervals. The coils are arranged to provide additive fields at the center of the coils where a

sample (such as a finger or test tube) is to be located. These coil pairs act as the energization or realignment coil and as the sensor, in a manner similar to the surface coil described hereinbefore. This arrangement is believed to provide better signal discrimination by increasing the signal-to-noise ratio. The coils are mounted in a housing similar to that shown in Figs. 1 and 2 and are controlled by a circuit and in the manner similar to that described in connection with Fig. 3. Physically, the standard and sample is inserted into one of the coils, such as the test tube 78 into coil 72. The portion to be tested is located at the center of the coils as shown. The coil pairs are interconnected by a delay line as shown in Fig. 7 so that they are electrically phased at 120° to each other.

The test sample is then tested as described above with coils first acting as the energization or realignment magnets and then as sensors or receivers. In other regards, such as signal processing and concentration analysis, this system operates in the same manner as above.

In those cases in which it may be desirable to implant a portion of the instrument, reference is made to Figs. 8 and 9.

A third embodiment 80 is shown in Fig. 8, which is constructed to surround a blood vessel which is internal of or within a body, for example, a vein or artery in the body.

The test device includes the principal magnet 82, which in this case is C-shaped and a pair of RF coils 84. The vein or artery 86 is positioned between the coil pairs and the poles of the magnet. By so doing, blood in the vein or artery is subjected to the first magnetic field, and the energization or realignment field is provided and relaxation is sensed by coils 84.

In a fourth embodiment, the test instrument 90 is constructed for surgical implantation as shown in Fig. 9.

Such a device has two component parts: one part is the internal or implanted portion 92 and the other part is the external or power supply and sensing part 94. The two parts are electronically coupled by transformer-like members as described herein.

In the fourth embodiment 90 an external AC power supply 96 is inductively coupled to an internal power supply 98. The internal power supply 98 powers the NMR unit 100, which is connected to probe and magnet unit 102. Signals from the probe and magnet are received by the receiver 104, which is inductively coupled to the microprocessor 106 through the coil element 108. The microprocessor then provides an output to the digital display 110 of the glucose concentration.

The magnet and probe assembly 102 is in the same form as that in Fig. 8 and is positioned to surround an artery. The signal processing is performed by the microprocessor in the same manner as with the other embodiments, particularly Fig. 3.

In a fifth embodiment, a surface blood vessel, usually a vein, is distended and used to analyze for glucose concentration. Such an embodiment is shown in Figs. 10 and 11, where a patient's arm 120 is shown surrounded by a pressurizable cuff 122 for causing a vein 124 to protrude or distend from the skin surface. In that situation, the NMR unit is fitted on either side of the protruding vessel at the surface of the arm. In this embodiment a C-shaped permanent magnet 126 is arranged so that its north and south poles (N & S) are on opposite sides of the vessel. A surface coil 128, like that in Figs. 1-2, is employed for energization and realignment and sensing. Testing circuitry of the type shown in Fig. 3 is also employed in the embodiment of Figs. 10 and 11.

A principal advantage of the test instrument shown herein is that the device is smaller than the large NMR test instruments now used at hospitals, etc. The reason is that the present instruments include a large principal magnet for surrounding the body of a patient. Here, since the tested portion is a finger or other extremity, the principal magnet may be smaller so that the instrument may be mounted on a table top, carried in a brief case, or be even smaller. In order to achieve such a device, the magnet must be small in size, be of a comparatively light weight, such as one pound (450 g), and still exhibit an adequate field strength. Adequate strengths should be on the order of at least five to six kilogauss. One particularly suitable material containing Neodymium is manufactured by General Motors Corporation.

Fig. 12 shows the generator and gate 46 and the receiver and gate 48, respectively, connected to separate transmit and receive coils 38', and 38".

Fig. 13 shows an embodiment of the coils 38' and 38" along with the field directions, including the bias field H_0 , at 90° with respect to one another.

Figs. 14 and 15 illustrate the use of a plurality of surface coils 38", which are connected for additive fields, as a single transmit/receive arrangement.

Fig. 16 shows an alternative bias magnet, similar to that shown in Fig. 11. The magnet 130 comprises a pair of spaced pole pieces 132, 134, which define a gap for receiving, in this example, a finger.

Although the invention has been described with respect to preferred embodiments, it is not to be so limited, as changes and modifications can be made which are within the full intended scope of the invention.

as defined by the appended claims.

Claims

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1. A nuclear magnetic resonance spectroscopy apparatus for testing body fluids for the presence of constituents, in which a first magnetic field aligns ^1H protons to an initial position, and in which a second magnetic field is cyclically energized and deenergized by circuit means to cause alignment of the ^1H protons to a second position and realignment to said initial position, and in which the magnetic changes resulting during realignment are detected and analyzed, the improvement comprising:
 - 10 first magnet means for creating said first magnetic field comprising a pair of permanent bar magnets each including a north pole and a south pole,
 - second magnet means for creating said second magnetic field,
 - mounting means for mounting said first magnet means,
 - 15 said mounting means comprising a pair of spaced apart members for positioning said pair of bar magnets spaced apart with the north pole of each said bar magnets secured to one of said members and the south pole of each said bar magnets secured to the other of said members, said first magnet means, said second magnet means and said mounting means providing a cavity defining a test region therein for receiving a vessel or body extremity to be tested,
 - 20 said first magnetic field being substantially uniform in field strength and direction throughout said test region;
 - said second magnet means being operatively disposed with respect to said test region for being magnetically coupled to the body fluid to be tested;
 - first and second end members connecting said pair of spaced apart members, said first end member including an aperture therethrough for access of said vessel or body extremity into said test region;
 - 25 circuit means for detecting and analyzing said magnetic changes;
 - said second end member having switch means operatively associated therewith for initiating operation of said circuit means;
 - a sample holder containing a standard sample of known concentrations of the constituents to be investigated;
 - 30 said standard sample holder being normally disposed in said test region;
 - means for biasing said sample holder to urge said sample holder toward said first end member and to normally locate said standard sample in said test region and capable of being operatively coupled to said second magnet means when said second magnet means is energized;
 - 35 and said switch means being actuated in response to the movement of said sample holder out of said test region to operate said switch means when said vessel or said body extremity to be tested is moved into said test region.

2. Apparatus as claimed in claim 1, wherein:

- 40 each of said spaced apart members comprises a pole piece directed into said test region to concentrate the magnetic flux.

3. Apparatus as claimed in claim 1 or 2, wherein:

- said second magnet means comprises surface coil means, said surface coil means having a plurality of additively connected surface coils for both transmitting energization and sensing.

4. Apparatus as claimed in claim 1 or 2, wherein:

- 45 said second magnet means comprises surface coil means, said surface coil means having coils phased at 120° for both transmitting energization and sensing.

5. A nuclear magnetic resonance apparatus for spectroscopic testing of body fluids for the presence of a constituent, said apparatus comprising:

- 50 principal magnet means partially defining a test region and having a pair of opposed magnetic poles establishing a substantially uniform field within the test region;
- coil means; and
- circuit means coupled to said coil means for producing an energization and realignment field within the test region and for detecting changes resulting from relaxation of said field, and for analyzing said changes;
- said apparatus being portable and said principal magnet means being positioned to receive and test said
- 55 body fluid in a vessel or in a body extremity between said poles and in said test region;
- said coil means being constructed to be positioned adjacent to said extremity or vessel to be tested; and
- said circuit means including means for energizing said coil means to resonate ^1H protons adjacent said coil means, means for sensing the change as indicated by a spectrum having peaks corresponding to various

molecular bonds.

said circuit means also including means for comparing the actual amplitude of a peak for a first constituent in the body fluid being tested to a predetermined amplitude for a peak for a predetermined quantity of said first constituent contained in a second, standard sample and for determining the actual value of a second constituent in said body from a predetermined relationship between predetermined values of the peaks for the first and second constituents.

6. An apparatus as in claim 5, wherein the first constituent is water and the second constituent is glucose, and including means for calculating and displaying the actual concentration of glucose as determined from the following relationship:

Glucose concentration = K (mg/dl)
(mg/dl)

15 x $\frac{(\text{Glucose patient peak height})}{(\text{Glucose standard peak height})}$

20 x $\frac{(\text{Water standard peak height})}{(\text{Water patient peak height})}$

25 wherein

K = concentration of glucose in said standard sample expressed in mg/dl.

30

7. An apparatus as in claim 5, wherein the first constituent is water and the second constituent is alcohol, and including means for calculating and displaying the actual concentration of alcohol as determined from the following relationship:

Alcohol concentration = K (mg/dl)
(mg/dl)

40 x $\frac{(\text{Alcohol patient peak height})}{(\text{Alcohol standard peak height})}$

45 x $\frac{(\text{Water standard peak height})}{(\text{Water patient peak height})}$

wherein

50 K = concentration of alcohol in said standard sample expressed in mg/dl.

55 8. An apparatus as in claim 5, 6 or 7 wherein said coil means comprises at least one surface coil positioned adjacent the extremity or vessel to be tested.

9. An apparatus as in claim 5, 6, 7 or 8 wherein said coil means comprises a transmitting coil and receiving coil.

10. An apparatus as in any of claims 5 to 9, wherein the test region in said device is constructed to test a human finger in the area below the fingernail and the surface coil is arranged to be positioned in close proximity to said test region; and said apparatus also includes a standard sample to be tested for calibration purposes after testing of the finger.

5 11. An apparatus as in claim 10, wherein the fluid to be tested is blood serum, and the first constituent is water and second constituent is glucose and said standard sample contains a mixture of water and glucose of known concentration.

12. An apparatus as in claim 11, wherein the apparatus includes means for resiliently biasing a standard sample holder into the test region adjacent said surface coil and for movement into a second position by
10 movement of the finger to be tested into said test region.

13. An apparatus as in claim 12, wherein said coil energizing means is activated responsive to the movement of the standard sample holder.

14. An apparatus as in claim 10, wherein said body extremity is a finger and the test apparatus is constructed to surround said finger and the coil is constructed to be positioned adjacent said finger.

15 15. An apparatus as in claim 5, for use in testing the body fluid in a blood vessel in vivo wherein the poles of the principal magnet are constructed to be positioned on opposite sides of the blood vessel.

16. An apparatus as in claim 15, wherein the blood vessel is a blood vessel of an animal and said coil means is a surface coil.

17. An apparatus as in claim 15, wherein said apparatus is implantable and said secondary magnet
20 comprises a pair of coils adapted to be positioned on opposite sides of a vessel.

18. An apparatus as in claim 5, wherein said secondary magnet comprises three coil pairs whose axes are in the same plane and equally spaced from each other and which intersect at a center so that their fields are at 120° spacing, said testing sample being adapted to be positioned at the center of said pairs.

19. An apparatus as in any of claims 5 to 18, wherein said circuit means includes memory means for
25 storing an operational program, and microprocessor means coupled to a display means and to said memory means, for selectively activating said coil means for processing signals received by said coil means, for comparing actual test values of said body fluid sample with predetermined test values and for displaying test results in accordance with the stored program.

20. An apparatus as in claim 19, wherein said apparatus includes disabling switch means for disabling
30 said memory means in the event an unauthorized access to said apparatus is attempted.

21. A method for noninvasively determining the value of a constituent in a body fluid using nuclear magnetic resonance spectroscopy, the method comprising the step of: analyzing a sample of said body fluid comprising the substeps of:

(a) exposing said body fluid sample to a biasing magnetic field, providing at least one magnetic field
35 pulse to decrease the water peak in said body fluid sample, resonating a magnetic field across said body fluid sample, sampling the field and recording data from the field and storing a spectrum of chemical shifts versus peak height as the patient data;

(b) analyzing a standard sample having a known concentration of the constituent being tested for with the same fields as in substep (a), obtaining a standard sample pulse and recording data in memory and
40 storing a spectrum of chemical shifts versus peak height as standard sample data;

(c) checking operation of the system, including the steps of comparing the standard sample data for the constituent being tested with an acceptable standard sample spectrum previously recorded for said constituent for error within a normal tolerance;

(d) normalizing the patient data and standard sample data for equal water peaks, including the steps
45 of recalling the patient data and the standard sample data; adjusting the patient data peak height of water to match that of the standard data peak height of water; and

(e) calculating the body fluid sample constituent level comprising the substeps of obtaining a ratio of patient data constituent height to standard sample data constituent height and multiplying it by the concentration of said constituent in said standard sample to obtain a patient reading and displaying that
50 reading.

22. The method set forth in claim 21 wherein substeps (b) and (c) precede substep (a).

23. The method set forth in claim 22 wherein the analysis in substep (b) is done in the same sequence as that in substep (a).

24. The method set forth in claim 21, 22 or 23 wherein the body fluid is blood.

55 25. The method set forth in claim 24 wherein the constituent being tested for is glucose or alcohol.

26. A method for noninvasively determining in situ and in vivo the value of a constituent in a body fluid using nuclear magnetic resonance spectroscopy, said method comprising the steps of:
applying a biasing magnetic field to an extremity of a patient to align at least the ¹H protons in the body

- fluid to an initial orientation;
 applying a resonating field to flip the ^1H protons between a further position and the initial position;
 sensing magnetic changes as the bonds flip from the further position to the initial position as analog signals;
 converting the analog signals into digital signals;
 5 storing the digital signals as patient data in a memory;
 multiplying the accumulated responses in the memory by an exponential decay to improve line broadening;
 transforming the multiplied data with a fast Fourier transform;
 repeating the above steps for a standard sample which includes water and a predetermined amount of
 constituent being tested for;
 10 comparing the spectrum of chemical shifts versus peak height of the standard sample to stored data of a
 previous predetermined spectrum of the standard sample for allowable error;
 scaling the patient data peak height of water to match the peak height of the water of the standard sample
 data;
 forming a ratio of the patient data constituent peak height to the standard sample data constituent peak
 15 height;
 multiplying the ratio by known standard sample constituent/water ratio to obtain a patient constituent reading
 in designated units; and
 displaying the patient constituent level in such designated units;
27. A self-contained portable apparatus for performing *in situ* and *in vivo* nuclear magnetic resonance
 20 spectroscopy testing of body fluids for the presence of certain constituents therein, said apparatus
 comprising:
 wall means defining a housing;
 permanent magnet means disposed within said housing;
 said permanent magnet means at least partially defining a test region within said housing;
 25 means defining a relatively narrow access opening in said housing enabling access to said test region for
 the placement therein of a vessel containing a test sample of the body fluid to be tested,
 said test region being slightly larger than said vessel,
 said permanent magnet means creating a permanent magnetic field sufficiently effective to align to a first
 position ^1H protons of said test sample located in said test region;
 30 said permanent magnetic field being substantially uniform in field strength and direction throughout said test
 region;
 generator and first gate means for producing gated radio frequency pulses;
 coil means positioned within said housing and in close proximity to said test region, said coil means being
 connected to said generator, said first gate means being cyclically energized by the gated radio frequency
 35 pulses to cyclically flip the ^1H protons from said first position to a second aligned position, and for sensing
 the magnetic changes as analog data signals during realignment of said ^1H protons from said second
 position to said first position;
 receiving and second gate means connected to said coil means for receiving the analog data signals during
 realignment of said ^1H protons to said first position;
 40 analog/digital converter means connected to said receiving and second gate means for converting the
 analog data signals into digital data signals;
 control means connected to said generator and first gate means to receive data from said analog/digital
 converter, said control means comprising analysis means for storing and analyzing said digital data signals;
 and
 45 display means for displaying the results of said analysis to the user.

50

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FIG. 1

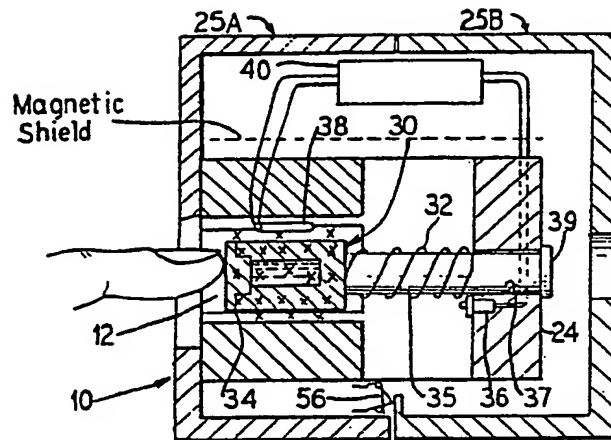
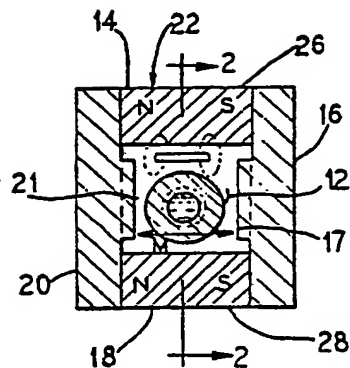


FIG. 2

FIG. 3

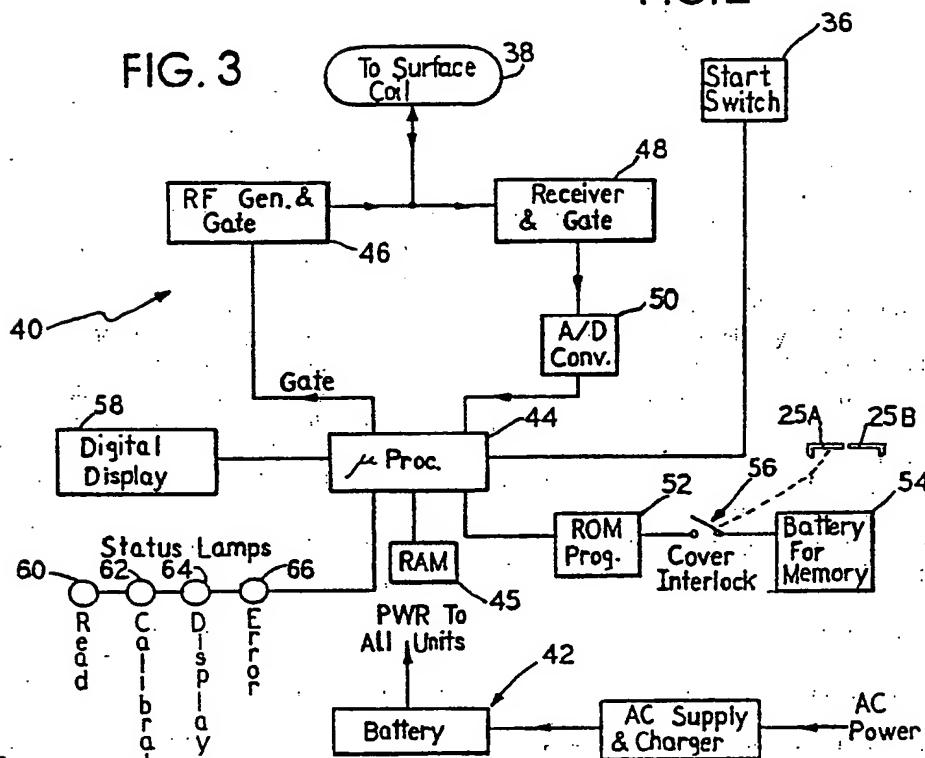


FIG. 4A

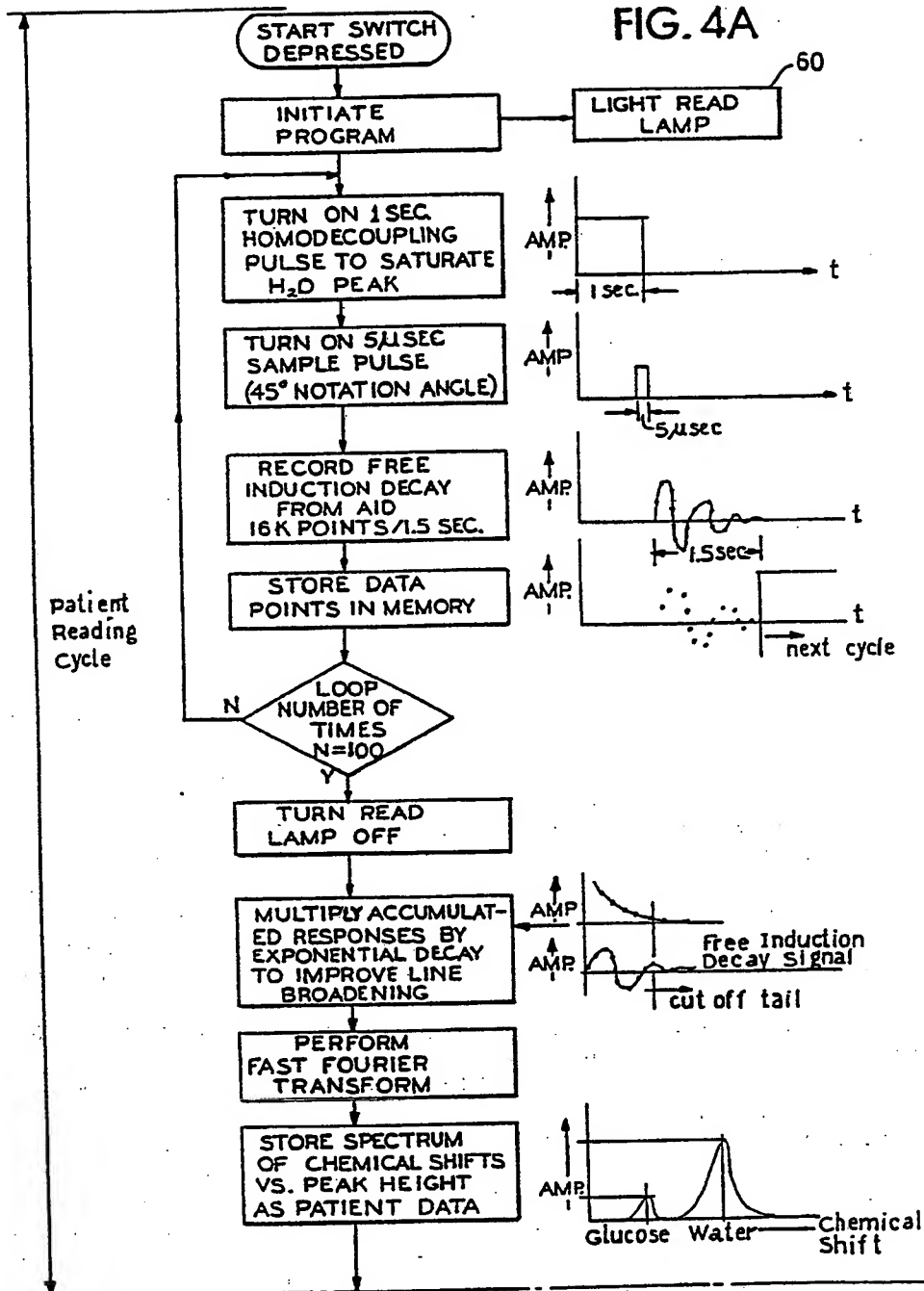


FIG. 4B

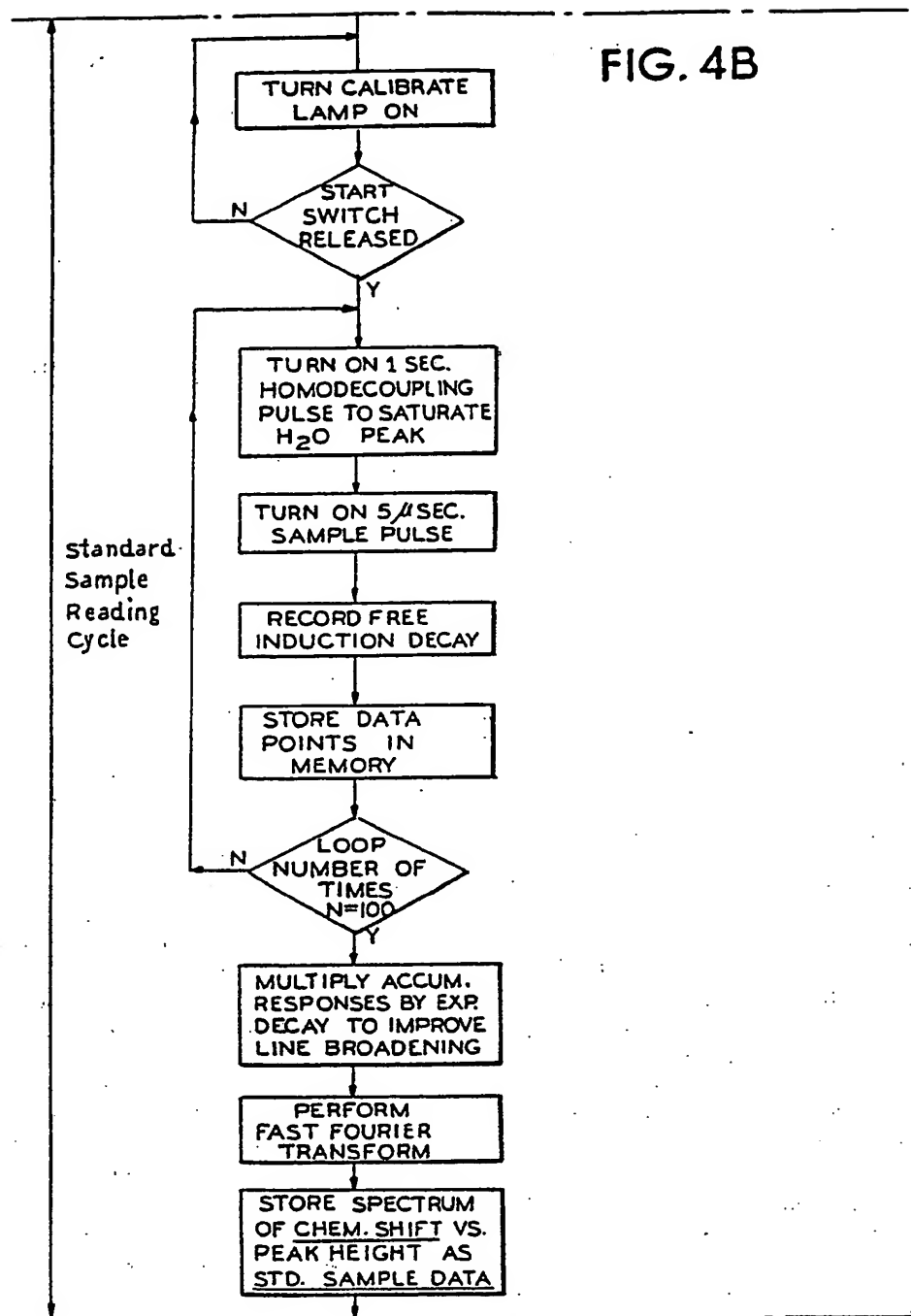


FIG. 4C

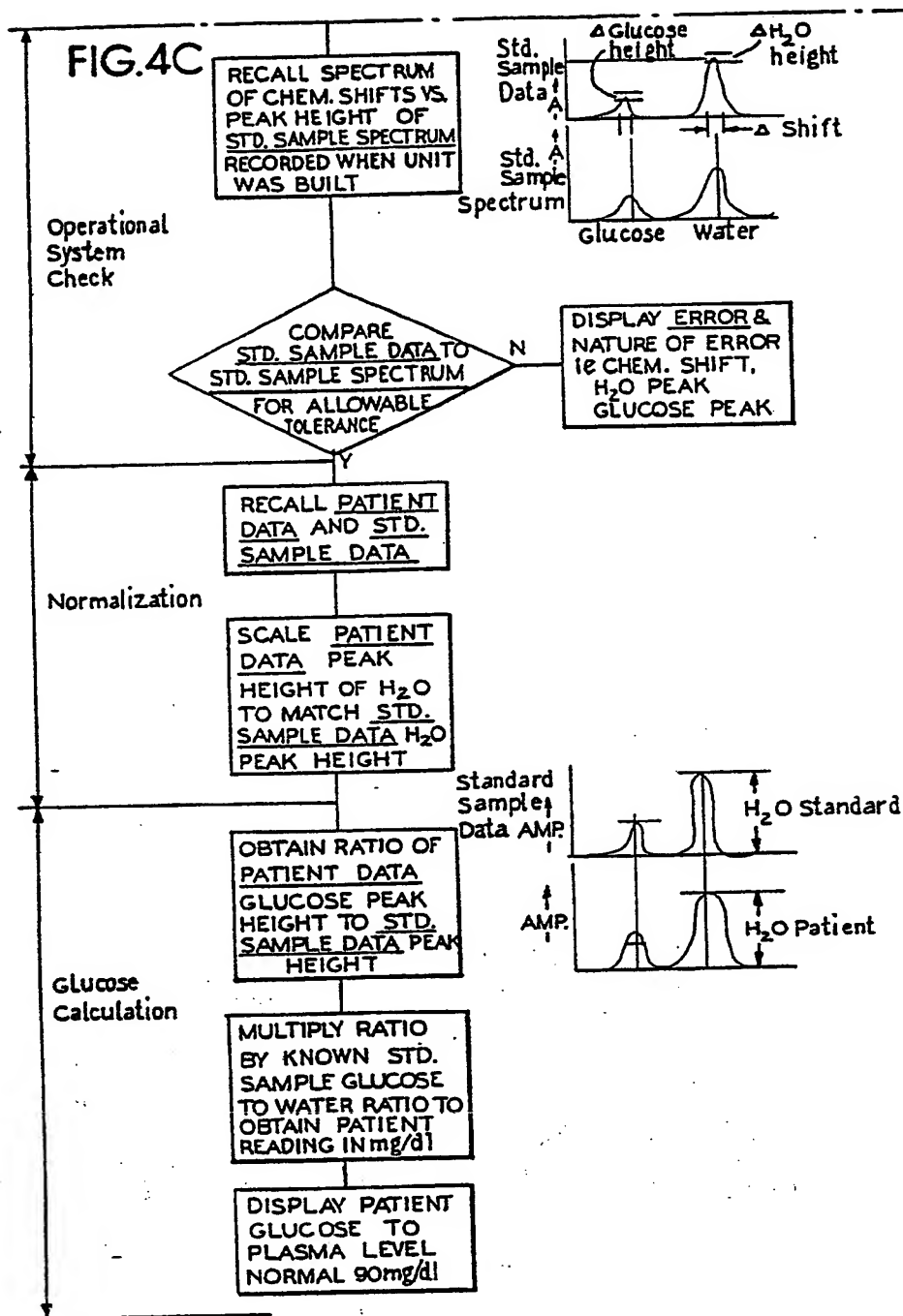


FIG. 5A

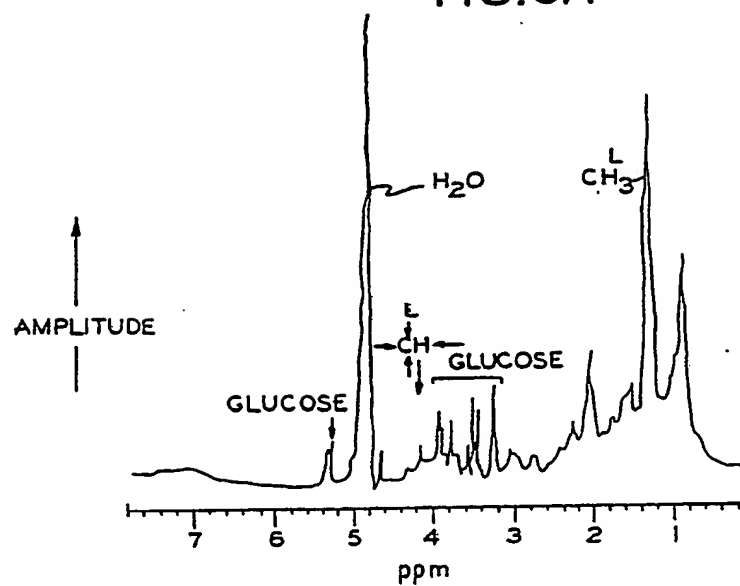
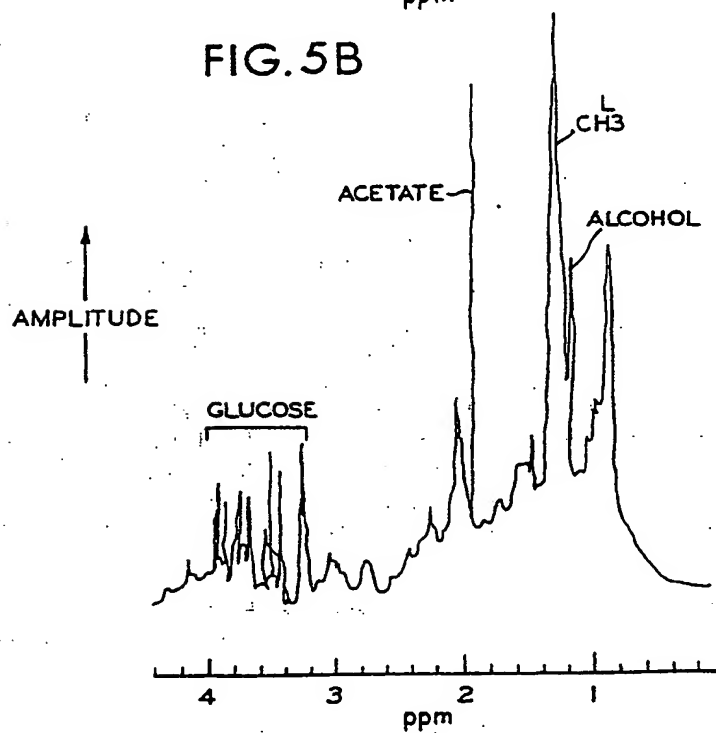
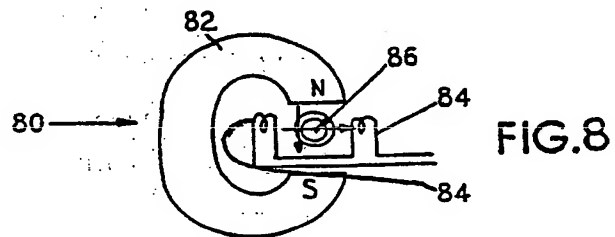
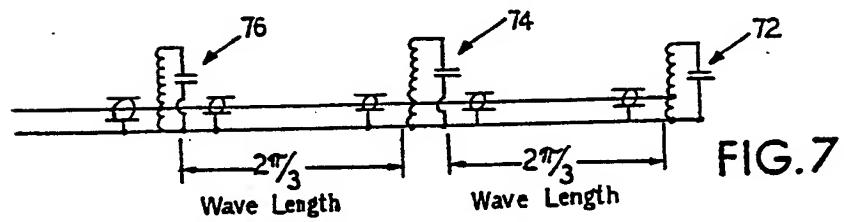
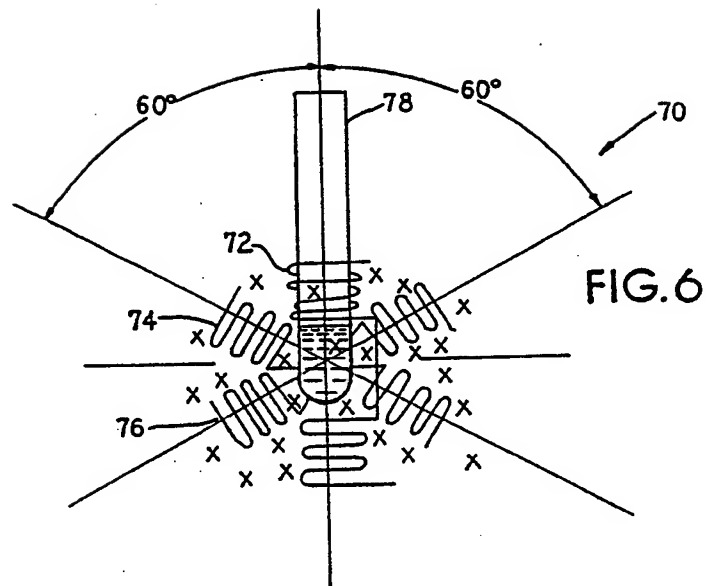
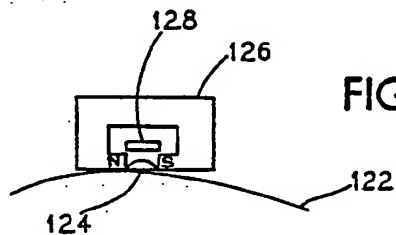
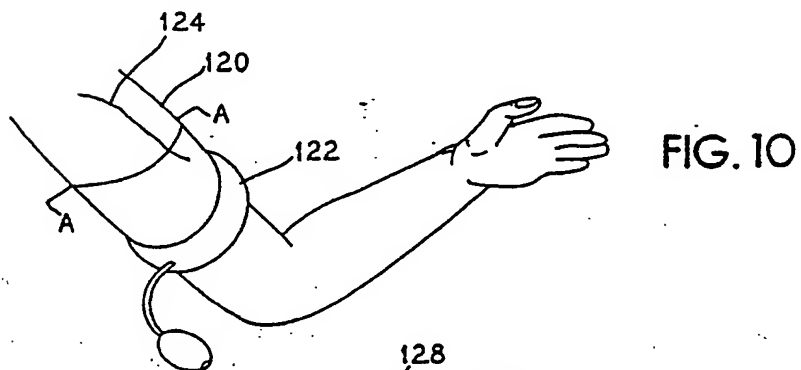
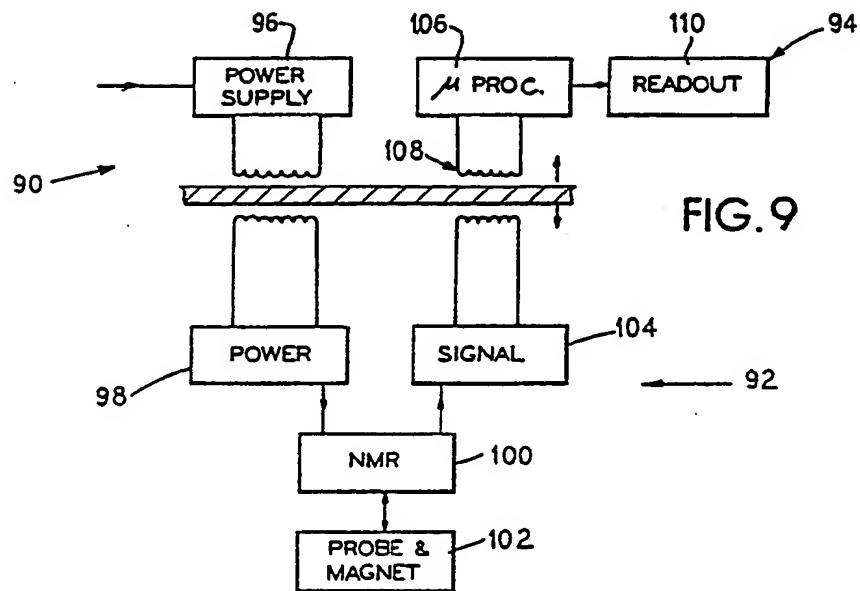
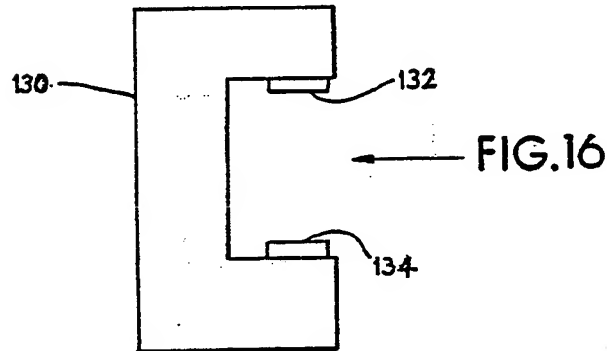
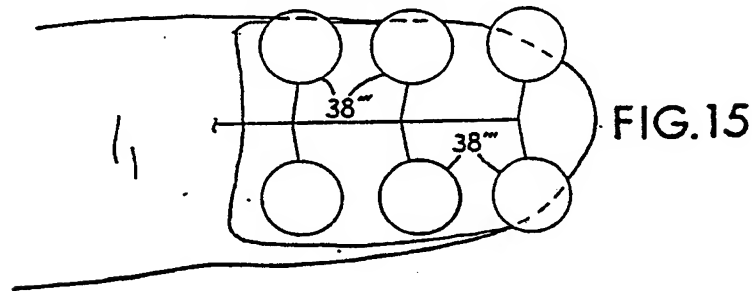
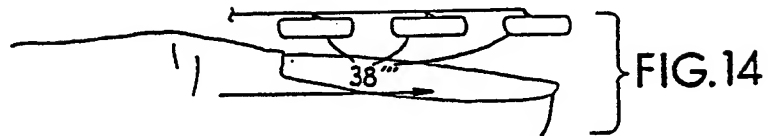
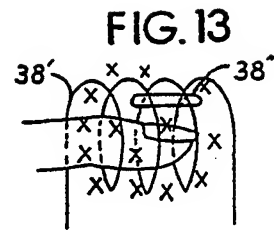
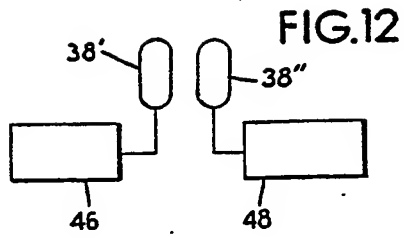


FIG. 5B









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EUROPEAN PATENT APPLICATION

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64 **Instrument and method for noninvasive testing for glucose and other body fluid constituents.**

67 There is disclosed herein a nuclear magnetic resonance apparatus (10) for testing body fluids for a constituent, for example, testing blood for glucose. The apparatus includes a principal magnet, a magnetizable coil (38), and a circuit (40) for energizing the coil for energizing and realigning molecules and detecting changes resulting from relaxing molecules and detecting changes resulting from relaxation of said field and analyzing said changes. The apparatus is compact and adapted to receive and test an extremity or vessel carrying a body fluid. The coil is constructed to be positioned adjacent the extremity or vessel to be tested. Circuit means are provided for energizing the coil to energize and realign molecules adjacent said coil, so as to permit molecules adjacent said coil to assume an aligned position and for sensing changes in position when the coil is deenergized, which is indicated by spectra having peaks corresponding to various molecular bonds. The circuit also includes means for comparing the actual value of a peak for a first constituent to a predetermined value for the peak of said first constituent and determining the actual value of a second constituent from a predetermined relationship between the values of the peaks for the first and

second constituents. Specifically, predetermined water and glucose peaks are compared with the measured water and glucose peaks for determining the measured glucose concentration.

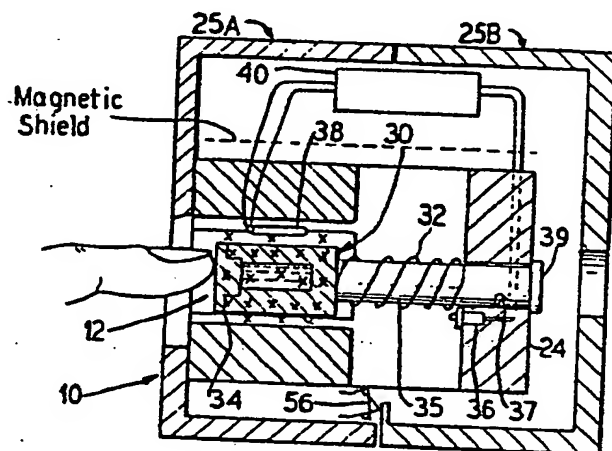


FIG. 2



European Patent
Office

EUROPEAN SEARCH REPORT

Application number

EP 88 30 6345

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	US-A-4 452 250 (CHANCE et al.) * Column 1, line 41 - column 2, line 8 *	1,3	G 01 N 24/08 A 61 B 5/05 G 01 R 33/30 G 01 R 33/46 G 01 R 33/34
A	US-A-4 240 439 (ABE et al.) * Column 1, lines 23-40; column 3, line 55 - column 6, line 52 *	1-3	
A	EP-A-0 227 898 (SIEMENS AG) * Column 1, line 45 - column 2, line 22 *	1,3	
A	US-A-4 030 483 (STEVENS) * Column 3, line 57 - column 4, line 42 *	1	
A	US-A-3 908 636 (PAGE) * Column 5, lines 7-23 *	1	TECHNICAL FIELDS SEARCHED (Int. Cl. 4) G 01 N 24/00 A 61 B 5/00 G 01 R 33/30 G 01 R 33/28 G 01 R 33/38 G 01 R 33/46
A	PATENT ABSTRACTS OF JAPAN, vol. 11, no. 22 (P-538)(2469), January 21, 1987 & JP-A-61 196 145 (TOSHIBA CORP.) 30-08-1986 * Abstract *	5,27	
A	US-A-4 389 613 (BROWN) * Column 1, lines 22-41; column 3, line 57 - column 4, line 24 *	5,19, 26	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 09-11-1989	Examiner DIOT
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			



European Patent
Office

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid.
namely claims:
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

X LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,
namely:

1. Claims 1-4: A NMR spectroscopy apparatus having switch means for initiating operating of circuit said switch means being actuated in response to the movement of a standard sample holder out of a test region
2. Claims 5-20, 26, 27: A NMR portable spectroscopy apparatus for performing in vivo, in situ measurement
3. Claims 21-25: A method for non invasively determining the value of a constituent in a body fluid

- ☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid.
namely claims:
- ☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.
namely claims:



EP 88 30 6345

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	MAGNETIC RESONANCE IN MEDICINE, vol. 5, 1987, pages 353-357; Academic Press Inc. T.L. RICHARDS et al.: "Measurement of lactate accumulation by in vivo proton NMR spectroscopy during global cerebral ischemia in rats" * Chapters "Methods" and "Results" * 5,8 --		
A	CLINICAL CHEMISTRY, vol.28, no. 9, 1982, pages 1873-1877; J.L. BOCK: "Analysis of serum by high-field proton nuclear magnetic resonance" * Chapter "Materials and Methods" * --	5,21, 24,25	
A	US-A-4 081 742 (HOFER et al.) * Column 5, line 14 - column 7, line 47 * --	21	TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
A	AMERICAN JOURNAL OF PHYSICS, vol. 44, no. 7, July 1976, page 655-657; Am. Ass. of Physics Teachers, New York, US L.W. RUPP et al.: "Miniature magnet for electron spin resonance experiments" * Whole article * --	5,26	
A	BIOCHIMICA ET BIOPHYSICA ACTA, vol. 886, 1986, pages 399-405, ref.no. BBA 11719; Elsevier Sc. Publ. B.V., Amsterdam, NL ./..		
The present search report has been drawn up for all claims			
Place of search		Date of completion of the search	Examiner
CATEGORY OF CITED DOCUMENTS			
X	particularly relevant if taken alone	T	theory or principle underlying the invention
Y	particularly relevant if combined with another document of the same category	E	earlier patent document, but published on, or after the filing date
A	technological background	D	document cited in the application
O	non-written disclosure	L	document cited for other reasons
P	intermediate document	&	member of the same patent family, corresponding document



EP 88 30 6345

- 3 -

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. -)
	S. WRAY et al.: "Direct in vivo measurement of absolute metabolite concentrations using ³¹ P nuclear magnetic resonance spectroscopy" * Page 401, paragraph "Experimental details" *	5, 26, 27	
			TECHNICAL FIELDS SEARCHED (Int. Cl. -)
The present search report has been drawn up for all claims			
Place of search		Date of completion of the search	Examiner
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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[7] The present invention relates to a method of determining the relative amounts of the components of a mixture, and more particularly to a method of determining the relative amounts of the components of a mixture by measuring the area under each peak in a chromatogram.

[7] The present invention relates to a method of determining the relative amounts of the components of a mixture, and more particularly to a method of determining the relative amounts of the components of a mixture by measuring the area under each peak in a chromatogram.

the present invention